A Comparison Between Fentanyl Plus Celecoxib And Epidural Anesthesia for Postoperative Pain Management Following Laparoscopic Gastrectomy

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ABSTRACT

Purpose To clarify the efficacy of postoperative pain management following laparoscopic gastrectomy (LG), we retrospectively compared pain assessments in patients who received fentanyl plus celecoxib with those who received epidural anesthesia.

Methods From 2011 to 2012, 55 consecutive LG patients at our institute received 48 hours of epidural anesthesia for postoperative pain management (Group-E). Since September 2013, epidural anesthesia was replaced with 24 hours of intravenous fentanyl and 4 days of oral celecoxib. Thirty-three consecutive LG patients who received this analgesic method (Group-FC) were included in this analysis. The severity of postoperative pain as assessed by the FACES Pain Rating Scale and the frequency of rescue pain medication were retrospectively compared between the two groups.

Results No significant difference in the severity of postoperative pain on postoperative day (POD) 0 or 1 was observed between the two groups. In contrast, pain was significantly lower in Group-FC than Group-E on POD 2, 3, 4, and 7. The total use of rescue pain medications during the first 7 days following LG did not differ between the two groups.

Conclusion Pain management using 24 hours of intravenous fentanyl and 4 days of oral celecoxib is comparable to epidural anesthesia following LG.

Introduction

Laparoscopic distal gastrectomy (LDG) has been widely accepted as a minimally invasive and safe procedure for operating on gastric cancer located in the middle and lower stomach [1, 2]. Prospective randomized clinical studies have reported better cosmesis and postoperative quality of life, less postoperative pain and complications, shorter hospital stay, and faster postoperative recovery following LDG compared with open gastrectomy [3-5]. Moreover, although laparoscopic total gastrectomy (LTG) is a technically challenging procedure, LTG is increasingly being performed and is reported to be a safe and effective treatment for upper gastric cancer [6-8].

Epidural anesthesia is widely used to provide postoperative pain relief following major abdominal surgery, including laparoscopic gastrectomy (LG). Epidural anesthesia has been reported to decrease cardiovascular, pulmonary, and gastrointestinal morbidities, especially in high-risk patients, compared with systemic opioids [9-11]. However, the use of epidural anesthesia for minimally invasive procedures, such as laparoscopic cholecystectomy and laparoscopic colorectal surgery, has been limited because the benefits compared with systemic opioids were not evident [12]. In addition, the use of epidural anesthesia carries the rare but serious risk of neurologic complications such as abscess and hematoma, which may leave permanent damage [13]. The risk for epidural hematoma can be further increased by prophylactic anticoagulant therapy, which is used to prevent lethal pulmonary embolism

following surgery. The use of epidural anesthesia also carries other potential risks of complications, including multiple punctures, which can increase the patient's stress and pain; dural puncture, which can cause a stubborn headache; improper insertion, which requires the removal of the tube; and hypotension [14].

Since September 2013, our institute revised our pain management following LG from 48 hours of epidural anesthesia to 24 hours of intravenous fentanyl and 4 days of oral celecoxib, because we consider that the analgesic effect of epidural anesthesia is not necessarily needed for patients requiring LG and could be replaced with non-steroidal anti-inflammatory drugs (NSAIDs), which play an important role in analgesia following colorectal surgery [15]. Here we aimed to evaluate the efficacy of this new analgesic protocol on postoperative pain in a retrospective comparative study.

Materials & Methods

Patients

We retrospectively reviewed individual medical records from our institute. This was a bi-center study, in which a total of eight surgeons performed LG. However, the same surgeon, who is qualified by the Japanese endoscopic surgical skill qualification system [16] and whose experience includes more than 500 laparoscopic gastric resections, was associated with all operations as either an operator or instructive assistant. From January 2011 to

December 2012, 55 consecutive patients who underwent LG for gastric cancer received 48 hours of epidural anesthesia for postoperative pain management (Group-E). During this period, the indication for the use of LG for gastric cancer was limited to preoperative clinical stage I and II disease, irrespective of the patient's past history of laparotomy. From September 2013 to December 2014, 33 consecutive patients who underwent LG for gastric cancer received 24 hours of intravenous fentanyl and 4 days of oral celecoxib (Group-FC) postoperatively. This conversion to postoperative pain management without epidural anesthesia was launched after obtaining the agreement of the anesthesiologists at our institute. During this period, the indications for using LG for gastric cancer remained unchanged. However, our indications changed in April 2013, at which time they were extended to include clinical stage III disease, irrespective of the patient's past history of laparotomy. There were no changes in operative procedures, including size of the ports and length of the incisions, throughout the entire study period from 2011 to 2014. Patients in both groups were excluded from this study if they were assessed as 3 or higher according to the American Society of Anesthesiologists (ASA) Physical Status scoring system; required the simultaneous resection of another organ due to synchronous primary malignancy at another site; or had undergone reduced port surgery. The extent of lymph node dissection and the cancer stage were classified according to the Japanese classification of gastric carcinoma [17] and the 2010 Japanese gastric cancer treatment guidelines [18].

Operative procedure

Patients were placed in the lithotomy position. The LDG procedure was performed using five ports: two 5-mm bilateral costal arch ports, two 12-mm bilateral flank ports, and one 12-mm camera port in the umbilical region. For stomach extraction, either a 4-cm upper abdominal incision was made or the camera port wound was extended to 4 cm. Reconstruction was selected on the basis of the patient's condition: Billroth I anastomosis was selected in thin patients and Roux-en-Y anastomosis was selected in overweight patients. The port sites to the LTG procedure were the same as for the LDG, except that the camera port wound was extended to 4 cm for stomach extraction, and Roux-en-Y reconstruction was performed laparoscopically as previously described [6].

Intraoperative anesthesia

General anesthesia was induced with propofol and fentanyl, and rocuronium bromide was administered to facilitate endotracheal intubation. Anesthesia was maintained in both groups with desflurane or sevoflurane, remifentanil, and additional rocuronium bromide. For Group-E, the anesthesiologist inserted a continuous epidural catheter at T7/8 or T8/9 immediately before induction. A 1% lidocaine infusion was administered at 3-5 ml/h via this catheter during surgery. Just before wound closure, a 0.25% bupivacaine infusion was

initiated at 2 ml/h via the epidural catheter. In contrast, flurbiprofen or acetaminophen was administered immediately prior to wound closure in the FC group. No patient in either group received any other local anesthetic block, including a transversus abdominis plane block or wound infiltration.

Clinical pathway

Postoperative care was provided to all patients according to the same clinical pathway: walking and drinking water were resumed on postoperative day (POD) 1, a water-soluble contrast (100 ml of meglumine sodium amidotrizoate) for the examination of anastomosis was administered on POD 3, meals were resumed on POD 4, and hospital discharge was permitted on POD 10 when the postoperative course was favorable.

Pain management and assessment

In the Group-E patients, 2 ml/h of 0.25% bupivacaine was infused continuously into the epidural space by balloon infusion pump for 48 hours postoperatively. In the Group-FC patients, 20 μg/h of fentanyl was administered intravenously for 24 hours postoperatively. In addition, oral administration of celecoxib (400 mg/day) for 4 days from POD 1 was started while patients were still receiving fentanyl. To evaluate the degree of pain in both groups, the Wong-Baker FACES Pain Rating Scale was used as previously described [19, 20]. Each

patient was evaluated from POD 1 to POD 4 and on POD 7, and changes in pain were compared between the two groups. The FACES Pain Rating Scales were recorded three times per day, and the highest score of the day was used in the analysis. Flurbiprofen, pentazocine, and acetaminophen were administered intravenously as rescue pain medication upon patient request in both groups.

Statistical analysis

Data were expressed as the mean ± standard deviation and compared between Group-E and Group-FC using the Student's t-test and Chi-square test (with Yates' correction when necessary). Statistical analyses were performed using StatMate IV for Windows (ATMS Co., Tokyo, Japan), and $p<0.05$ was considered statistically significant.

Results

Clinical characteristics of the patients

The clinical characteristics of the patients from both groups are shown in Table 1. There were no significant differences between Group-E and Group-FC with respect to age, gender, body mass index (BMI), ASA classification, and history of previous laparotomy. The preoperative clinical stage was significantly higher in Group-FC than Group-E (Table 1).

Operative procedures and outcomes

The operative procedures and outcomes are shown in Table 2. The proportion of patients who underwent LDG and LTG was not significantly different between the two groups. Ten patients underwent concomitant cholecystectomy due to symptomatic cholelithiasis and five patients underwent concomitant splenectomy for prophylactic D2 lymph node dissection; these procedures did not require additional port insertions. Group-FC included significantly more patients who underwent D2 lymph node dissection than Group-E. As a result, the duration of surgery was longer and the number of dissected lymph nodes was higher in Group-FC compared with Group-E (Table 2). In contrast, intraoperative blood loss, postoperative complications, and the length of the postoperative hospital stay were not significantly different between the two groups. According to the Clavien-Dindo classification [21], grade III or higher postoperative complications occurred in one patient in Group-FC

(3.0%, one intraabdominal abscess requiring percutaneous drainage) and one patient in Group-E (1.8%, one intraabdominal abscess requiring percutaneous drainage); no significant difference was observed between the two groups. No patients deviated from the clinical pathway, except for the two patients who experienced a grade III or higher postoperative complication.

Postoperative pain assessed by the FACES Pain Rating Scale

The results of the postoperative pain assessments are shown in Fig. 1A. Pain on POD 0 and 1 as assessed by the FACES scale did not differ significantly between the two groups: POD 0, 1.5±1.1 in Group-FC and 1.3±1.1 in Group-E (p=0.651): and POD 1, 1.8±1.1 in Group-FC and 1.9±1.2 in Group-E (p=0.651). In contrast, pain was significantly lower in Group-FC than Group-E on POD 2 (Group-FC: 1.4±0.9, Group-E: 2.0±1.2, p=0.019), POD 3 (Group-FC: 1.1±0.9, Group-E: 1.7±0.9, p=0.003), POD 4 (Group-FC: 0.5±0.7, Group-E: 1.4±0.8, p<0.001), and POD 7 (Group-FC: 0.2±0.8, Group-E: 0.4±0.6, p=0.001). Pain gradually decreased in Group-FC, and patients reported an average pain score of less than 1 on POD 4. In contrast, patients in Group-E did not report an average pain score of less than 1 until POD 7.

Usage of rescue pain medication

The number of doses of rescue pain medication used each day from POD 0 to POD 3 is shown in Fig. 1B: POD 0, 0.6±0.9 in Group-FC and 0.5±0.7 in Group-E (p=0.265); POD 1, 1.6±1.6 in Group-FC and 0.7±0.8 in Group-E, (p=0.002); POD 2, 0.8±1.3 in Group-FC and 1.2±1.4 in Group-E (p=0.091); and POD 3, 0.4±1.0 in Group-FC and 0.7±1.2 in Group-E (p=0.074). After POD 4, rescue pain medication use was 0.4±1.0 in Group-FC and 0.4±0.8 in Group-E, respectively (p=0.464). Differences were only significant between groups on POD 1, when Group-FC received more doses. Total use of rescue pain medication for the first 7 postoperative days was also similar between the two groups, as shown in Fig. 1C (Group-FC, 3.9±4.4 versus Group-E 3.6±4.0; p=0.721).

Adverse effects

In 32 (97.0%) of the 33 Group-FC patients, intravenous fentanyl (20 μg/h) was administered continuously for 24 hours without any mild to severe adverse effects. In one female, intravenous fentanyl was discontinued because of dizziness and nausea but not vomiting. Celecoxib (400 mg/day) was administered orally for 4 days after surgery in all patients; no patients experienced severe adverse effects. No patient experienced any adverse effects related to epidural anesthesia, including nausea or hypotension. The postoperative blood analysis between the two groups is shown in Table 3. There were no significant differences in white blood cell counts between the two groups except on POD 1. Similarly, the

levels of hemoglobin, serum aspartate transaminase, serum creatinine, serum albumin, and serum C-reactive protein did not differ significantly between the two groups. These findings indicate that the oral administration of celecoxib for 4 days did not adversely affect other body systems or organs, such as the hematologic system, liver, or kidney. There were also no signs of obvious gastrointestinal bleeding. In addition, perioperative vital signs, including body temperature, systolic blood pressure, and pulse, were not significantly different between the two groups, as shown in Fig. 2.

Discussion

The results of this retrospective study suggest that postoperative pain management using fentanyl followed by celecoxib is equivalent or superior to epidural anesthesia following LG. Although pain assessments on POD 0 and 1 were not significantly different between the two groups, patients in Group-FC reported significantly lower pain than patients in Group-E on POD 2. These findings suggest that the effect of intravenous fentanyl on pain is equivalent to the effect of epidural anesthesia, and that the addition of oral celecoxib provided further pain relief among patients in Group-FC. On POD 3, epidural anesthesia had already been stopped in Group-E, whereas oral celecoxib administration was continued in Group-FC. Therefore, we expected to observe less pain among patients in Group-FC after POD 3. However, our results demonstrated that Group-FC reported less pain even on POD 7. These findings suggest that continuing postoperative pain management for 4 days after surgery may lead to better long-term pain relief. In contrast, the number of doses of rescue pain medication on POD 1 in Group-FC was greater than that of Group-E, whereas usage of rescue pain medications on POD 0, on POD 2 and later, and during the entire 7-day postoperative period were not significantly different between the two groups. These findings suggest that the analgesic effects of fentanyl plus celecoxib in the first 2 days after surgery are similar to or possibly weaker than those of epidural anesthesia, although this was not reflected in the pain scores. Nevertheless, the fentanyl plus celecoxib combination produced

satisfactory pain relief from POD 2. Our results confirm that pain management with fentanyl plus celecoxib is considered to be reliable for analgesia following LG.

In this study, fentanyl was administered until the blood concentration of celecoxib reached effective levels. The use of opioids following surgery is known to increase the risk of postoperative nausea and vomiting in a dose-dependent manner [22]. Despite the use of a relatively low dose of fentanyl (20 μg/h) in this study, one (3.0%) female patient was discontinued from intravenous fentanyl due to its adverse effects. Therefore, the use of fentanyl carries some risk of nausea independent from the dose. Fortunately, this patient immediately recovered once fentanyl was discontinued, and did not deviate from the clinical pathway. However, to maintain high quality postoperative pain control and minimize adverse effects, opioid-free analgesia should be considered. For example, the continuous administration of bupivacaine into the preperitoneal space following LDG has been reported to provide effective pain relief [23]. Intravenous lidocaine and transversus abdominis plane block also may be considered for postoperative analgesia, as previously reported for other abdominal surgeries [24, 25]. Further investigation is necessary to determine the ideal postoperative pain management for patients.

We selected celecoxib as the main analgesic NSAID in this study. Celecoxib is a selective COX-2 inhibitor that is rapidly absorbed, possesses good oral bioavailability, and has a short mean plasma half-life. The analgesic effect of celecoxib has been demonstrated in

both orthopedic and obstetric surgery [26-29]. Our findings indicate that all patients tolerated 4 days of celecoxib, and as a result, celecoxib provided stable pain relief following LG without any severe adverse effects in the liver, kidney, gastrointestinal tract, or hemocytes. Therefore, we consider postoperative celecoxib as a feasible short-term therapy for postoperative pain control following LG. However, attention must be paid to the possibility of an increased risk for celecoxib-induced cardiovascular events or renal injury with long-term administration [30, 31].

Our data showed no significant differences in perioperative vital signs and postoperative cardiovascular or pulmonary complications between the two groups, which indicates that epidural anesthesia failed to provide any advantages as previously described [12]. Epidural anesthesia did not provide a significantly superior analgesic effect compared with fentanyl plus celecoxib therapy. In addition, there are some technical risks associated with epidural anesthesia, including multiple punctures, hematoma, and dural puncture, as well as an increased risk of infection associated with long-term placement [13, 14]. Because there are no technical difficulties and few side effects associated with the administration of intravenous fentanyl and oral celecoxib, this postoperative analgesic therapy seems to have significant advantages over epidural anesthesia with respect to both analgesic effects and the risk of adverse effects.

A limitation of this study was that it was retrospective and included only a small

number of patients. Another limitation was that the efficacy of the epidural anesthesia was low due to the low dose (2 ml/h) of bupivacaine. Additional pain relief may have been provided by a higher dose or in combination with NSAIDs. However, we considered the level of pain control by epidural analgesia to be adequate because patients with epidural analgesia did not rate themselves as higher than a score of 2 on the FACES scale, which is considered to be the threshold at which rescue analgesia should be used. Accordingly, 2 ml/h of bupivacaine appears to be the minimum effective dose for pain management by epidural analgesia. In addition, there were several differences in clinical factors between the two groups, including the clinical cancer stage, extent of lymph node dissection, and duration of surgery. Group-FC included more patients with an advanced stage of cancer, and who underwent D2 lymph node dissection. As a result, the duration of surgery was significantly longer in Group-FC compared with Group-E. Together, these findings indicate that patients in Group-FC required more invasive surgery. However, despite these unfavorable conditions, postoperative pain in Group-FC was equivalent or superior to that in Group-E. This result suggests that celecoxib and fentanyl are adequate replacements for epidural analgesia in LG. Large-scale randomized clinical trials are necessary to clarify the efficacy of this postoperative pain management strategy as an alternative to epidural anesthesia.

In conclusion, our postoperative management strategy using 24 hours of fentanyl and 4 days of celecoxib was safe and effective in providing pain relief following LG. We believe

that fentanyl plus celecoxib therapy is sufficiently potent to replace epidural anesthesia for pain management following minimally invasive surgery.

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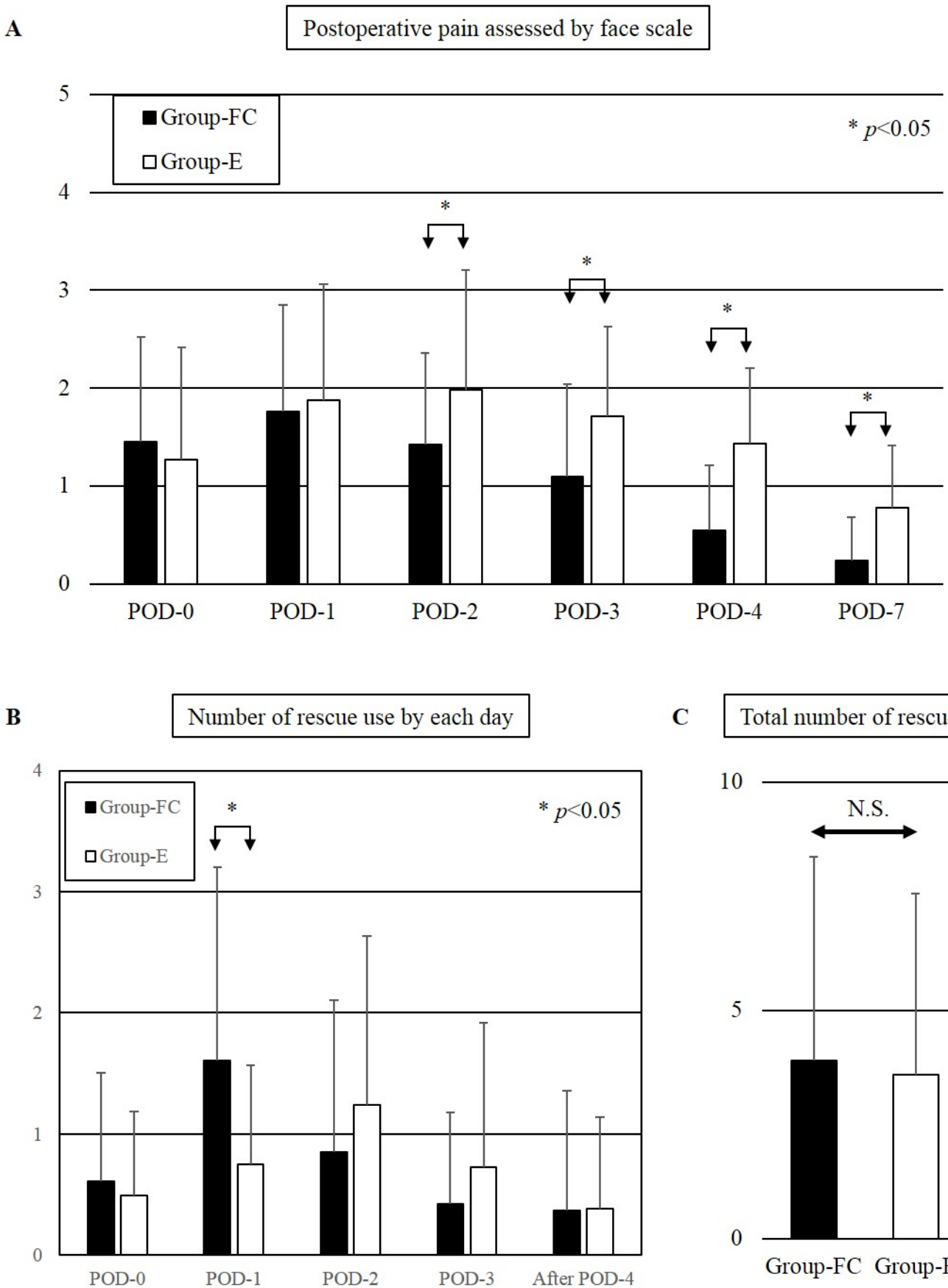
Figure Legends

Figure 1. A. The results of the postoperative pain assessments in both groups are shown (* $p<0.05$). **B.** The number of doses of rescue pain medication each day in both groups is shown (* $p<0.05$). **C.** The total number of rescue pain medication doses during the first 7 postoperative days in both groups is shown (* $p<0.05$). Flurbiprofen, pentazocine, and acetaminophen were administered intravenously as rescue medications for postoperative pain at the request of the patient.

Figure 2. The perioperative measurements of maximum body temperature (**A**), maximum systolic blood pressure (**B**), and maximum pulse (**C**) in both groups are shown. There were no significant differences in perioperative vital signs between the two groups.

Fig. 1.


A
Postoperative pain assessed by face scale
Group-FC
Group-E
* p<0.05
5
4
3
2
1
0
POD-0
POD-1
POD-2
POD-3
POD-4
POD-7
B
Number of rescue use by each day
Group-FC
Group-E
* p<0.05
POD-0
POD-1
POD-2
POD-3
After POD-4
C
Total number of rescue use
N.S.
10
5
0
Group-FC
Group-E

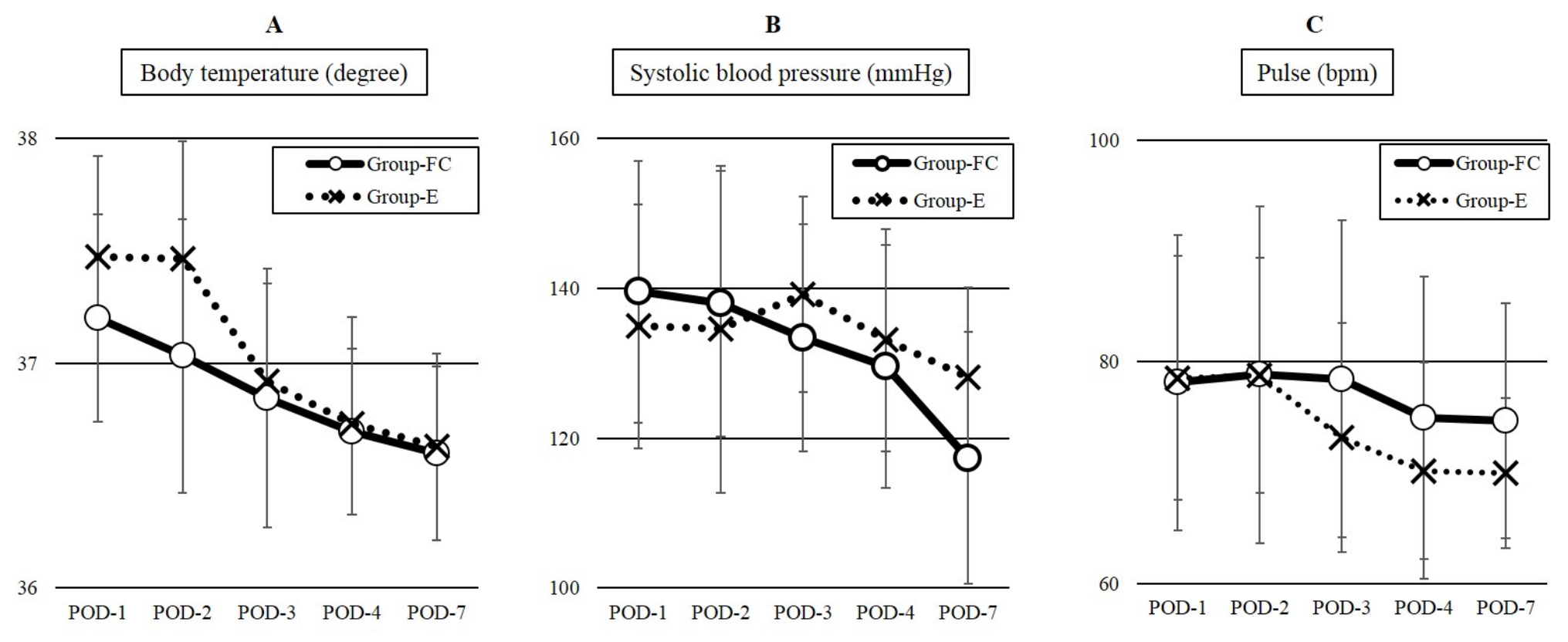

A
Body temperature (degree)
38
37
36
Group-FC
Group-E
POD-1
POD-2
POD-3
POD-4
POD-7
B
Systolic blood pressure (mmHg)
160
140
120
100
Group-FC
Group-E
POD-1
POD-2
POD-3
POD-4
POD-7
C
Pulse (bpm)
100
80
60
Group-FC
Group-E
POD-1
POD-2
POD-3
POD-4
POD-7

Table 1. Baseline characteristics of the patients

	Group-FC (N=33)	Group-E (N=55)	*p*-value
Age (years)	67.0 ± 11.0	68.6 ± 8.7	0.469
Gender			
Male	20 (60.6%)	37 (67.3%)	0.526
Female	13 (39.4%)	18 (32.7%)	
BMI (kg/m^2)	23.3 ± 3.8	23.1 ± 3.6	0.716
ASA classification			
1	10 (30.3%)	23 (41.8%)	0.280
2	23 (69.7%)	32 (58.2%)	
Previous laparotomy of upper abdomen			
Present (number of patients)	1 (3.0%)	4 (7.3%)	0.721
Preoperative clinical stage			
Stage I	14 (42.4%)	39 (70.9%)	*0.008*
≥Stage II	19 (57.6%)	16 (29.1%)	

ASA: American Society of Anesthesiologists; BMI: body mass index.

Table 2. Surgical procedures and outcomes

	Group-FC (N=33)	Group-E (N=55)	*p*-value
Surgical procedures			
LDG	25 (75.8%)	43 (78.2%)	0.793
Billroth-I	18 (54.5%)	26 (47.3%)	
Roux-en-Y	7 (21.2%)	17 (30.9%)	
LTG	8 (24.2%)	12 (23.3%)	
Lymph node dissection			
D1	2 (6.1%)	3 (5.4%)	*0.014*
D1+	18 (54.5%)	45 (81.8%)	
D2	13 (39.4%)	7 (12.7%)	
Concomitant organ resection	8 (24.2%)	7 (12.7%)	0.272
Gallbladder (number of patients)	4	6	
Spleen (number of patients)	4	1	
Surgical outcomes			
Duration (minutes)	267 ± 57	230 ± 57	*0.004*
Blood loss (ml)	77 ± 97	79 ± 159	0.857
Number of dissected lymph nodes	44.5 ± 14.3	35.4 ± 15.5	*0.008*
Postoperative complications (Clavien-Dindo Grade III or higher)	1 (3.0%)	1 (1.8%)	0.712
Intraabdominal abscess (number of patients)	1	1	
Hospital stay (days)	12.1 ± 4.3	13.1 ± 6.2	0.386

LDG: laparoscopic distal gastrectomy; LTG: laparoscopic total gastrectomy.

Table 3. Postoperative blood analysis

	Group-FC (N=33)	Group-E (N=55)	*p*-value
White blood cell counts (/mm^3)			
POD 1	10418 ± 4059	8535 ± 2245	*0.031*
POD 4	7085 ± 3681	6083 ± 1585	0.147
POD 7	6382 ± 2617	5652 ± 1995	0.146
Hemoglobin (g/dl)			
POD 1	11.92 ± 1.68	12.08 ± 1.63	0.678
POD 4	11.79 ± 1.63	11.93 ± 1.29	0.669
POD 7	12.04 ±1.79	11.98 ± 1.46	0.861
Aspartate transaminase (IU/l)			
POD 1	122 ± 91	104 ± 62	0.323
POD 4	28 ± 16	30 ± 20	0.508
POD 7	34 ± 16	53 ± 84	0.096
Creatinine (mg/dl)			
POD 1	0.76 ± 0.25	0.80 ± 0.26	0.535
POD 4	0.70 ± 0.21	0.73 ± 0.25	0.609
POD 7	0.82 ± 0.24	0.83 ± 0.26	0.882
Albumin (g/dl)			
POD 1	3.30 ± 0.95	3.37 ± 0.36	0.286
POD 4	3.21 ± 0.48	3.37 ± 0.39	0.099
POD 7	3.41 ± 0.53	3.53 ± 0.36	0.232
C-reactive protein (mg/dl)			
POD 1	3.55 ± 2.19	4.08 ± 2.26	0.287
POD 4	7.13 ± 5.71	7.75 ± 6.43	0.654
POD 7	3.78 ± 4.12	3.10 ± 2.91	0.406